Postoperative Radiotherapy After Radical Prostatectomy: Let’s Work Together to Tackle the Known Unknowns

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The debate on the timing of postoperative radiotherapy (RT) after radical prostatectomy (RP) usually focuses on the choice between early adjuvant treatment and deferred salvage treatment. There have been numerous retrospective studies of postoperative RT. In this month’s issue of European Urology, Pfister et al. present a pooled analysis of 10 such studies, having considered no fewer than 115 for inclusion in their analysis [1].

1. Retrospective studies of postoperative radiotherapy timing

Retrospective comparisons of outcomes for these two contrasting approaches are of limited value. A major problem is the inherent bias between the groups: Those receiving deferred salvage RT have confirmed recurrent disease, whereas many of those receiving adjuvant RT would have been cured by surgery alone. Consequently, the outcome of adjuvant RT will always appear better than that of salvage RT.

Pfister et al. have focussed on the outcome of deferred salvage RT when given “early,” which they define as a prostate-specific antigen (PSA) level of <0.5 ng/ml. Reviewing the retrospective studies, they report that even within this low range of PSA levels, the lower the pre-RT PSA, the better the subsequent biochemical control. As they acknowledge, this finding is hard to interpret. It certainly seems plausible that men with more aggressive recurrent disease will have more rapidly rising postoperative PSA, and so, by the time they get salvage RT, their PSA levels will be higher than those of men with less aggressive recurrent disease. Retrospective studies cannot avoid this bias. Having said that, we agree with the authors’ conclusion that when using salvage RT, it seems prudent to give it early, as soon as PSA failure is detected [1].

2. Prospective randomised controlled trials

The gold standard of evidence-based medicine is the randomised controlled trial (RCT) with balanced patient groups, prospective data collection, and clearly defined outcome measures. Retrospective studies cannot substitute for prospective RCTs in this setting, yet there have been remarkably few completed prospective RCTs of postoperative RT in prostate cancer (PCa)—just three, to be precise. This parlous situation compares unfavourably with other common cancers. For example, as long ago as 1995, a meta-analysis was published of 36 RCTs of postoperative RT in breast cancer. It is hardly surprising that PCa specialists still cannot agree on the optimal timing for postoperative RT. For that matter, they also cannot agree on the most appropriate target volume, the ideal dose, or the role of adjuvant hormone therapy whenever postoperative RT is used!

3. Results from randomised trials of postoperative radiotherapy timing

What can we learn from the three RCTs that have been completed?

3.1. SWOG 8794

Patients were eligible for the Southwest Oncology Group trial [2] if they had extracapsular extension, seminal vesicle involvement, or positive margins at RP. Starting in 1988, 425 men were randomised to immediate RT to the prostate...
bed versus observation. The primary outcome measure was metastasis-free survival (MFS): metastases or any death. Ten-year MFS was 71% for adjuvant RT versus 61% for observation (hazard ratio [HR]: 0.71; 95% confidence interval [CI], 0.54–0.94; \( p = 0.016 \)). Overall survival (OS) was a secondary outcome measure and also favoured adjuvant RT (HR: 0.72; 95% CI, 0.55–0.96; \( p = 0.023 \)). The trial was small, and only 57 men reported metastatic disease (20 of 214 in the adjuvant RT arm, 37 of 211 in the observation arm), so metastases accounted for about a quarter of MFS events (57 of 207). Treatment for PCa can only be expected to treat PCa, but around three-quarters of deaths may be attributed to other causes. Therefore, the OS benefit should be regarded with caution. It is quite possible that a chance imbalance in non-PCa deaths could have contributed to the observed survival benefit.

### 3.2. EORTC 22911

The European Organisation for Research and Treatment of Cancer trial had a similar design and recruited 1005 patients, and the latest update had a median follow-up of 10.6 yr [3]. The primary outcome measure was biochemical progression-free survival, which favoured adjuvant RT rather than observation (HR: 0.49; 95% CI, 0.41–0.59; \( p < 0.0001 \)). This outcome measure shows activity for RT but, unfortunately, is of little use for clinical decision making because biochemical progression is the point at which early salvage RT would be initiated. More important, there was no statistically significant difference in longer-term outcome measures, notably, PCa mortality (HR: 0.78; 95% CI, 0.46–1.33; \( p = 0.34 \)) and OS (HR: 1.18; 95% CI, 0.91–1.53; \( p = 0.20 \)).

### 3.3. ARO 96-02

Uniquely, ARO 96-02 was restricted to men with undetectable PSA after RP. It is therefore a comparison of truly adjuvant postoperative RT versus an observation policy. Starting in 1997, it recruited a modest 307 patients. Updated results were presented at the American Society of Clinical Oncology’s Genitourinary Cancers Symposium in 2013, but even at a median follow-up of 9.5 yr, this RCT remains immature with respect to clinically meaningful end points, with only 43 deaths and 45 MFS events reported [4]. The number of patients developing metastatic disease was not given. Based on such small numbers, this RCT contributes less to the evidence about the relative efficacy of adjuvant versus salvage RT.

Taken together, the three reported RCTs of postoperative RT do not provide clear evidence of benefit in long-term outcome measures for adjuvant treatment with respect to freedom from metastasis or survival. The optimal timing of postoperative RT remains an important, unresolved question.

### 4. Ongoing trials of postoperative radiotherapy timing

There is a pressing need for further RCTs to resolve the issue of early adjuvant RT versus deferred salvage RT. Three such trials are ongoing: RADICALS-RT (ClinicalTrials.gov identifier NCT00541047) [5], RAVES (ClinicalTrials.gov identifier NCT00860652), and GETUG-17 (ClinicalTrials.gov identifier NCT00667069). More information about the trials is available through trial registries including ClinicalTrials.gov.

All three trials have similar designs. They are true adjuvant trials, recruiting men with high-risk disease at RP with a postoperative PSA <0.2 ng/ml. Men in the control arm all receive prompt salvage RT in the event of rising PSA. The combined accrual to these trials has reached >1200 patients, and a pooled analysis is planned to address the important question of whether or not adjuvant RT improves OS compared with a salvage RT policy.

Rather than add any further to the extensive literature on retrospective studies, we urge PCa clinicians to focus their efforts towards supporting each of these ongoing RCTs. We have a responsibility to future PCa patients. Indeed, many of us will be such patients. It is unacceptable that our field lags more than 20 yr behind that of breast cancer. Together, our prospective RCTs will define the new standard.

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### References